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09/995,100	11/27/2001	Kunio Hori	15111	3176

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,100	HORI ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *7-10,14-20,23,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-13,21,22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/2004 and 11/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Groups I, claims 1-6, 11-13, 21, 22, and 24 in the reply filed on October 4, 2004 is acknowledged. The traversal is on the ground(s) that: (1) "[G]roup I and Group II employ substantially identical method steps of optically measuring and analyzing a marker substance in the course of a reaction, as in the methods of Group III. Clearly, all these embodiments define one single inventive concept. Thus, Groups I-III are very clearly interrelated and interdependent, not 'independent and distinct'."; (2) "[A]pplicants respectfully suggest that in view of the continued increase of official fees and the potential limitation of an applicant's financial resources, a practice which arbitrarily imposes restriction requirements may become prohibitive and thereby contravene the constitutional purpose to promote and encourage the progress of science and the useful arts. Moreover, under the regulatory changes as a consequence of the General Agreement on Trade and Tariffs (GAU), applicants are required to conduct simultaneous prosecution, as here, requiring excessive fling costs or otherwise compromise the term of related patent assets"; and (3) "basing restriction requirement on the classification system is improper".

The above arguments have been fully considered and have not been found persuasive toward the withdrawal of the restriction requirement nor persuasive toward the relaxation of same such that Groups I to III will be examined together. First, the examiner has clearly explained why Groups I, II, and III are independent and distinct inventions (see previous restriction requirement mailed on September 2, 2004) and restriction is based on search burden of Groups I, II, and III. Second, applicant does not explain why Groups I, II, and III define as

one single inventive concept. Third, the continued increase of official fees and the potential limitation of an applicant's financial resources and different classifications suggested by applicant are not the reason for the restriction. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Priority

2. Note that applicant filed certified copies of Japan application Nos. 2000-087500, 2000-87501, and 2000-087504 on November 27, 2001. However, there are no such documents in this instant application.

Specification

3. The disclosure is objected to because of the following informality: (1) there are two nucleotide sequences with more than ten nucleotides in Figure 10. However, there is no description of these nucleotide sequences in Brief Description of The Several Views of The Drawing and there is no SEQ ID NO for these nucleotide sequences; and (2) there are two nucleotide sequences with more than ten nucleotides in page 8 of the specification. However, there is no SEQ ID NO for these nucleotide sequences

Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claim 11 is rejected under 35 U.S.C. 102(e) as being anticipated by Jacobson *et al.*, (US 2003/0054356 A1, priority date: September 21, 2000).

Note that the priority date of this instant application is considered to be March 27, 2001 (its PCT filing date) since applicant does not provide English Translations for foreign priority papers (three Japanese Applications).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Regarding claim 11, since Jacobson *et al.*, teach a method for detecting a plurality of SNPs in nucleic acid molecules, wherein each SNP having two or more polymorphisms, comprising: (1) providing a plurality of populations of microspheres, wherein each population corresponds to a SNP and has an addressable signature, and wherein each of the microspheres in a population carries two or more fluorescently-labeled nucleic acid probes specific respectively to each of the polymorphisms for the SNP; (2) allowing the probes to hybridize to the SNPs, thereby forming SNP-probe pairs which are distinguishable by fluorescence intensity; and (3) determining the presence or absence and type of SNP via detecting the presence or absence and fluorescence intensity of the SNP-probe pairs and the corresponding microsphere signature wherein the probes on a microsphere are distinguishable from each other by their fluorescence intensity (see page 3, [0017] and page 17, claim 23), Jacobson *et al.*, disclose preparing a test

sample containing a polynucleotide, mixing a test sample with DNA probes PR_1 to PRn labeled with a detectable marker and capable of specifically binding to polymorphism sequences PS_1 to PSn (ie., two or more fluorescently-labeled nucleic acid probes specific respectively to each of the polymorphisms for the SNP), thereby binding the DNA probes PR_1 to PRn to the polynucleotide, detecting the DNA probes PR_1 to PRn in a micro space (ie., microsphere) and analyzing detection results to determine which one of the DNA probes PR_1 to PRn binds to the polynucleotide, thereby determining which one of the polymorphism sequences PR_1 to PSn corresponds to a nucleotide sequence of the polymorphism site as recited in steps (1) to (4) of claim 11.

Therefore, Jacobson *et al.*, teach all limitations recited in claims 11.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson *et al.*, (September 21, 2000) as applied to claim 11 above, and further in view of Tyagi *et al.*, (US Patent No. 6,150,097, filed on December 12, 1997) and Nakao *et al.*, (US Patent No. 6,589,740 B2, filed on March 9, 2001).

The teachings of Jacobson *et al.*, have been summarized previously, *supra*.

Regarding claim 1, since Jacobson *et al.*, teach a method for detecting a plurality of SNPs in nucleic acid molecules, wherein each SNP having two or more polymorphisms, comprising: (1) providing a plurality of populations of microspheres, wherein each population corresponds to a SNP and has an addressable signature, and wherein each of the microspheres in a population carries two or more fluorescently-labeled nucleic acid probes specific respectively to each of the polymorphisms for the SNP; (2) allowing the probes to hybridize to the SNPs, thereby forming SNP-probe pairs which are distinguishable by fluorescence intensity; and (3) determining the presence or absence and type of SNP via detecting the presence or absence and fluorescence intensity of the SNP-probe pairs and the corresponding microsphere signature wherein the probes on a microsphere are distinguishable from each other by their fluorescence intensity (see page 3, [0017] and page 17, claim 23), Jacobson *et al.*, disclose reacting a test sample containing polymorphism site (ie., one of nucleic acid molecules with one or more SNPs) with plurality types probes corresponding plurality types of polymorphism site to be identified said test sample (ie., fluorescently-labeled nucleic acid probes), said probes being labeled with marker substances so as to optically distinguish from each other (ie., the probes which are distinguishable by

fluorescence intensity) as recited in step (1) of claim 1. Since Jacobson *et al.*, teach that each of the fluorescently-labeled nucleic acid probes are specific respectively to each of the polymorphisms for the SNP (see page 3, [0017]) and "high affinity" is a relative term, Jacobson *et al.*, disclose that said probes binding to said plurality of types of the polymorphism site with a high affinity as recited in step (1) of claim 1.

Regarding claim 3, Jacobson *et al.*, teach that the polymorphism site is a single nucleotide polymorphism (see page 3, [0017]).

Jacobson *et al.*, do not disclose analyzing a positional change of the marker substance at a plurality of time points in the course of the reaction as recited in step (2) of claim 1.

Since Tyagi *et al.*, teach that, during the hybridization, the changes in fluorescence of each molecular beacon correspond to alteration of the position of the fluorescent dye on the molecular beacon (column 13) and Jacobson *et al.*, teach the hybridization by measuring the changes in fluorescence (see above), Jacobson *et al.*, as evidence by Tyagi *et al.*, disclose analyzing a positional change of the marker substance (ie., the fluorescent dye) as recited in step (2) of claim 1.

Nakao *et al.*, teach to determine the effect of temperature on nucleic acid hybridization by measuring the changes on the fluorescence on different time points (see column 2, lines 12-28).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 by analyzing a positional change of the marker substance at a plurality of time points in the course of the reaction in view of the patents of Jacobson *et al.*, Tyagi *et al.*, and Nakao *et al.*. One having ordinary skill in the art would have been motivated to do so because Nakao *et al.*, has

successfully determined the effect of temperature on nucleic acid hybridization by measuring the changes on the fluorescence on different time points and measuring the changes on the fluorescence on different time points would indirectly determine the effect of temperature on nucleic acid hybridization. One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 1 by analyzing a positional change of the marker substance at a plurality of time points in the course of the reaction.

8. Claims 2 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson *et al.*, (September 21, 2000) in view of Tyagi *et al.*, (1997) and Nakao *et al.*, (March 9, 2001) as applied to claims 1, 3, and 11 above, and further in view of Palo (US Patent No. 6,556,296 B1, priority date: September 29, 1997).

The teachings of Jacobson *et al.*, Tyagi *et al.*, and Nakao *et al.*, have been summarized previously, *supra*.

Jacobson *et al.*, Tyagi *et al.*, and Nakao *et al.*, do not disclose that said detecting is performed by a confocal microscope, and said analyzing is performed by a fluorescent correlation spectroscopy wherein said optical determining includes measuring fluctuation of the marker substance as recited in claims 2 and 21.

Palo teaches to measure fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope (see column 1, fourth paragraph and claims 1 and 19 in columns 9-11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 2 and 21 wherein said detecting is performed by a confocal microscope, said analyzing is performed by a fluorescent correlation spectroscopy and said optical determining includes measuring fluctuation of the marker substance (ie., the fluorescence dye) in view of the patents of Jacobson *et al.*, Tyagi *et al.*, Nakao *et al.*, and Palo. One having ordinary skill in the art would have been motivated to do so because Palo suggests that combination of a fluorescent correlation spectroscopy and a microscope during the process of measuring fluorescence would create a technology for monitoring fluorescence from single fluorophore molecules (see column 1, fourth paragraph). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claims 2 and 21 by measuring fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope.

9. Claims 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson *et al.*, (September 21, 2000) as applied to claim 11 above, and further in view of Nakao *et al.*, (March 9, 2001).

The teachings of Jacobson *et al.*, have been summarized previously, *supra*.

Regarding claim 4, since Jacobson *et al.*, teach a method for detecting a plurality of SNPs in nucleic acid molecules, wherein each SNP having two or more polymorphisms, comprising: (1) providing a plurality of populations of microspheres, wherein each population corresponds to a SNP and has an addressable signature, and wherein each of the microspheres in a population

carries two or more fluorescently-labeled nucleic acid probes specific respectively to each of the polymorphisms for the SNP; (2) allowing the probes to hybridize to the SNPs, thereby forming SNP-probe pairs which are distinguishable by fluorescence intensity; and (3) determining the presence or absence and type of SNP via detecting the presence or absence and fluorescence intensity of the SNP-probe pairs and the corresponding microsphere signature wherein the probes on a microsphere are distinguishable from each other by their fluorescence intensity (see page 3, [0017] and page 17, claim 23), Jacobson *et al.,* disclose hybridizing a test sample DNA fragment containing sequence of a polymorphism site (ie., one of nucleic acid molecules with one or more SNPs) with a plurality of types of DNA probes respectively having sequences complementary to a plurality of sequences be identified and contained in the test sample DNA fragment (ie., fluorescently-labeled nucleic acid probes), and labeled with a marker substance, said plurality of types probes being optically distinguish so as from each other (ie., the probes with different fluorescent labels) as recited in step (1) of claim 4.

Regarding claim 6, Jacobson *et al.,* teach that the polymorphism site is a single nucleotide polymorphism (see page 3, [0017]).

Jacobson *et al.,* do not disclose analyzing a change of the marker substance at a plurality of time points in the course of the reaction as recited in step (2) of claim 4.

Nakao *et al.,* teach to determine the effect of temperature on nucleic acid hybridization by measuring the changes on the fluorescence on different time points (see column 2, lines 12-28).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 by analyzing a change of the marker substance at a plurality of time points in the course of the reaction in

view of the patents of Jacobson *et al.*, and Nakao *et al.*. One having ordinary skill in the art would have been motivated to do so because Nakao *et al.*, has successfully determined the effect of temperature on nucleic acid hybridization by measuring the changes on the fluorescence on different time points and measuring the changes on the fluorescence on different time points would indirectly determine the effect of temperature on nucleic acid hybridization. One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 4 by analyzing a change of the marker substance at a plurality of time points in the course of the reaction.

10. Claims 5 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson *et al.*, (September 21, 2000) in view of Nakao *et al.*, (March 9, 2001) as applied to claims 4, 6, and 11 above, and further in view of Palo (1997).

The teachings of Jacobson *et al.*, and Nakao *et al.*, have been summarized previously, *supra.*

Jacobson *et al.*, and Nakao *et al.*, do not disclose that said detecting is performed by a confocal microscope, and said analyzing is performed by a fluorescent correlation spectroscopy wherein said optical determining includes measuring fluctuation of the marker substance as recited in claims 5 and 22.

Palo teaches to measure fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope (see column 1, fourth paragraph and claims 1 and 19 in columns 9-11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 5 and 22 wherein said detecting is performed by a confocal microscope, said analyzing is performed by a fluorescent correlation spectroscopy and said optical determining includes measuring fluctuation of the marker substance (ie., the fluorescence dye) in view of the patents of Jacobson *et al.*, Nakao *et al.*, and Palo. One having ordinary skill in the art would have been motivated to do so because Palo suggests that combination of a fluorescent correlation spectroscopy and a microscope during the process of measuring fluorescence would create a technology for monitoring fluorescence from single fluorophore molecules (see column 1, fourth paragraph). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claims 5 and 22 by measuring fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope.

11. Claims 12 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson *et al.*, (September 21, 2000) as applied to claim 11 above, and further in view of Palo (1997).

The teachings of Jacobson *et al.*, have been summarized previously, *supra*.

Jacobson *et al.*, do not disclose that said detecting is performed by a confocal microscope, and said analyzing is performed by a fluorescent correlation spectroscopy wherein said optical determining includes measuring fluctuation of the marker substance as recited in claims 12 and 24.

Palo teaches to measure fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope (see column 1, fourth paragraph and claims 1 and 19 in columns 9-11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 12 and 24 wherein said detecting is performed by a confocal microscope, said analyzing is performed by a fluorescent correlation spectroscopy and said optical determining includes measuring fluctuation of the marker substance (ie., the fluorescence dye) in view of the patents of Jacobson *et al.,* and Palo. One having ordinary skill in the art would have been motivated to do so because Palo suggests that combination of a fluorescent correlation spectroscopy and a microscope during the process of measuring fluorescence would create a technology for monitoring fluorescence from single fluorophore molecules (see column 1, fourth paragraph). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claims 12 and 24 by measuring fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope.

12. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson *et al.,* (September 21, 2000) as applied to claim 11 above, and further in view of Fujimiya *et al.,* (US Patent No. 5,190,632, published on March 2, 1993).

The teachings of Jacobson *et al.,* have been summarized previously, *supra.*

Jacobson *et al.,* do not disclose that said polynucleotide is a gene for a human

histocompatible antigen. However, Jacobson *et al.*, teach to perform their method using a polynucleotide from different sources (see page 5, [0044]).

Fujimiya *et al.*, teach that human histocompatible antigens have polymorphisms (see column 1, third paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 13 wherein said polynucleotide is a gene for a human histocompatible antigen in view of the patents of Jacobson *et al.*, and Fujimiya *et al.*. One having ordinary skill in the art would have been motivated to do so because Jacobson *et al.*, have showed that a polynucleotide from different sources are used in the method taught by Jacobson *et al.*, (see page 5, [0044]) and one having ordinary skill in the art at the time the invention was made would perform the method recited in claim 11 using a polynucleotide from different sources. One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 13 using a polynucleotide from a gene for a human histocompatible antigen.

Conclusion

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
November 3, 2004

FRANK LU
PATENT EXAMINER